MULTIPLE SCLEROSIS

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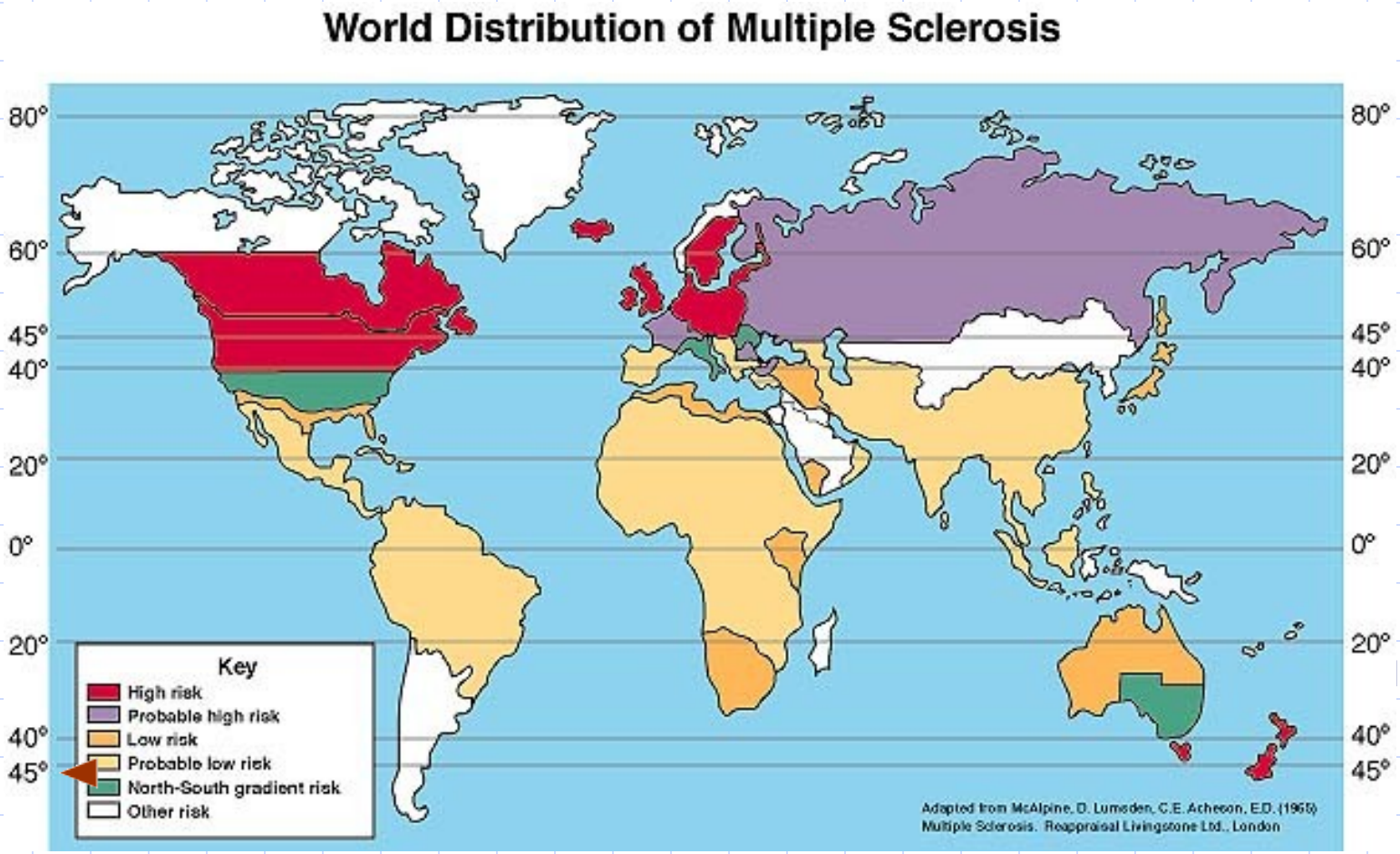
MULTIPLE SCLEROSIS

- Most common disabling condition in young adults
- Most common demyelinating disorder
- Chronic disease of the CNS
- Progresses to disability in majority of cases
- Unpredictable course / variety of signs and symptoms; sometimes mistaken for psych dx
- Current theory favors immunologic pathogenesis

ONSET

- 300,000 patients in N. America today
- Peak onset 20-30 years of age
- 70% have sxs between ages 21-40
- Rarely prior to age 10 or after age 60
- F > M (approx. 2:1)
- White > non-white (2:1)

GEOGRAPHIC DISTRIBUTION



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GENETICS

- Incidence in 1st degree relatives 20x higher than general population
- Monozygotic twins: 30% concordance
- Dizygotic twins: 5% concordance
- Linked to HLA A3, B7, DR2, DR3

PATHOLOGICAL HALLMARKS

- Described in late 1800s by Dr. Charcot
- Perivascular inflammation and demyelination
- Plaques occur anywhere in the CNS
  - Most frequent: optic nerve, brainstem, cerebellum, spinal cord
  - Above lesions correlate with clinical sxs
- Axon sparing within the plaques

PLAQUE EVOLUTION

- Disruption of blood-brain barrier
- Unknown if demyelination precedes or follows inflammation
- Acute inflammatory response of lymphocytes, plasma cells, macrophages
  - Macrophages contain myelin breakdown product
  - Lymphocytes: antibody- and cell-mediated immunity (direct), secretion of lymphokines or cytokines (indirect)

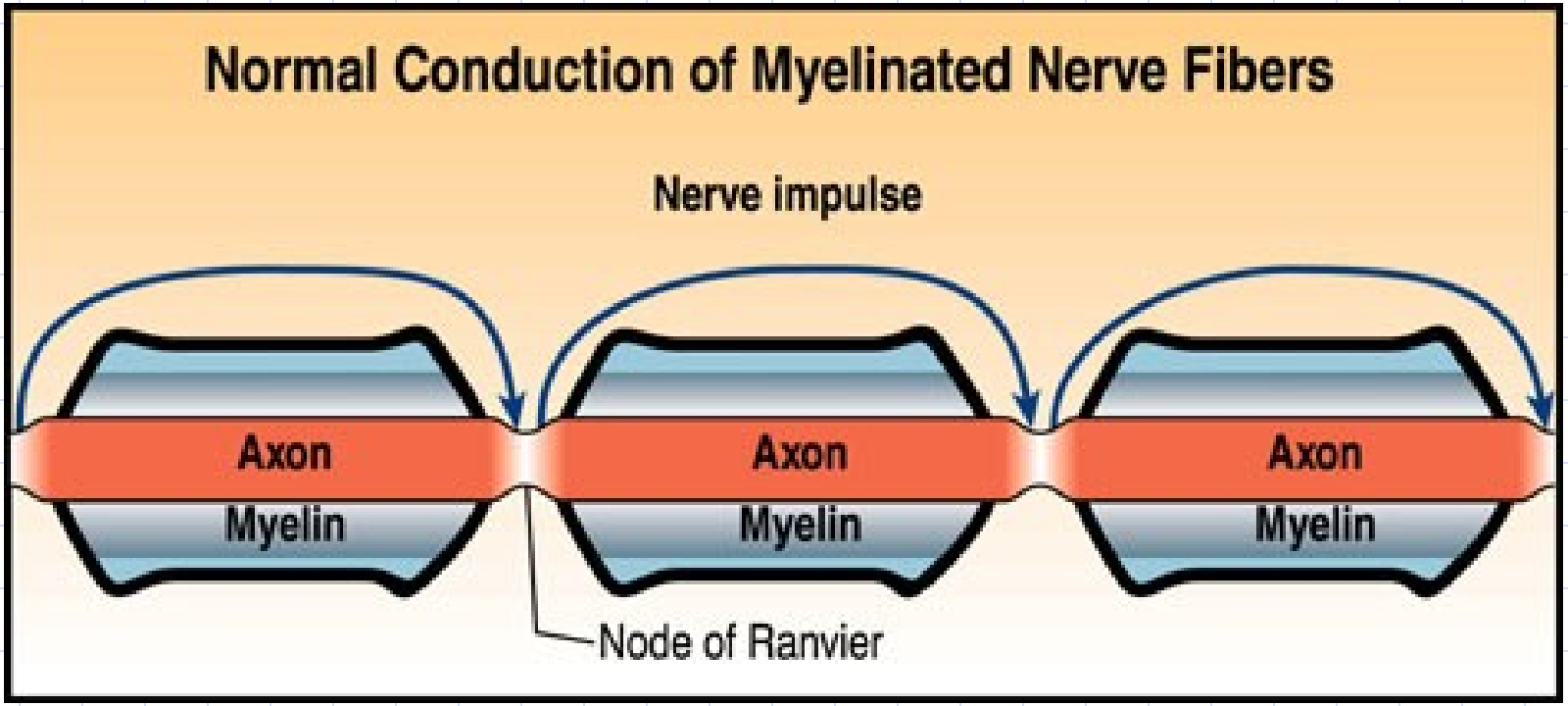
STRUCTURE OF PLAQUES

- Outer layers of myelin sheath separate
- Degenerative changes in myelin
- Infiltration with macrophages or microglia
- Preservation of axons
- Degree of oligodendrocyte preservation determines remyelination potential

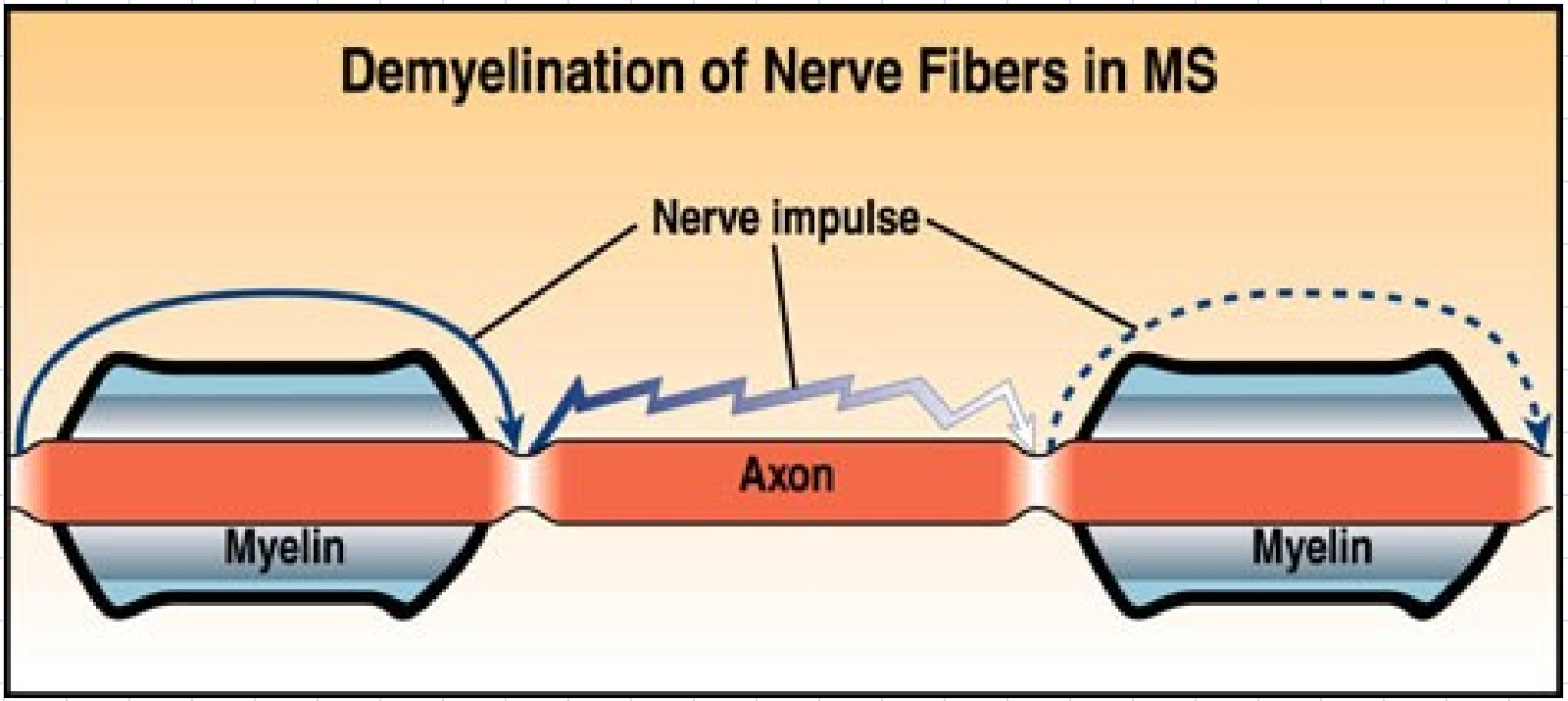
RESULTS OF DEMYELINATION

- Conduction block at site of lesion
- Slower conduction time along affected nerve
- Increased subjective feeling of fatigue secondary to compensation for neurologic deficits

NORMAL CONDUCTION



ABNORMAL CONDUCTION



ETIOLOGY

- Autoimmune
  - T-cells activate against myelin
- Viral
  - Specific viral protein not yet identified
  - Suspected “molecular mimicry”
  - Roseola (HHV6) associated with demyelination in MS patients
  - Viral infections known to provoke relapses

LABORATORY FINDINGS

- CSF
- Evoked potentials
- MRI
- Blood and urine

CSF

- Increased immunoglobulin concentration in >90% of patients
- IgG index (CSF/serum) elevated
- Oligoclonal bands—85%
- Elevated protein—50%
- Modest increase in mononuclear cells

EVOKED POTENTIALS

- VER (visual evoked response)—75% abnormal regardless of optic neuritis hx
- BAER (brainstem auditory evoked response)—30% abnormal
- SSER (somatosensory evoked response) – 80% abnormal
  - Helps distinguish peripheral from central lesions

MRI

- **Caveat: **
- Abnormal MRI without clinical evidence is not sufficient to confirm dx of MS…
- …Absence of abnormal MRI in clinically definite MS doesn’t disprove diagnosis

MRI FINDINGS

- Patchy areas of white matter in paraventricular cerebral areas
- Lesions in cerebellum/brainstem/ cervical and thoracic spinal cord
- Gadolinium enhancement identifies active lesions
  - Doesn’t correlate with increased disease activity

MRI – CONT'D

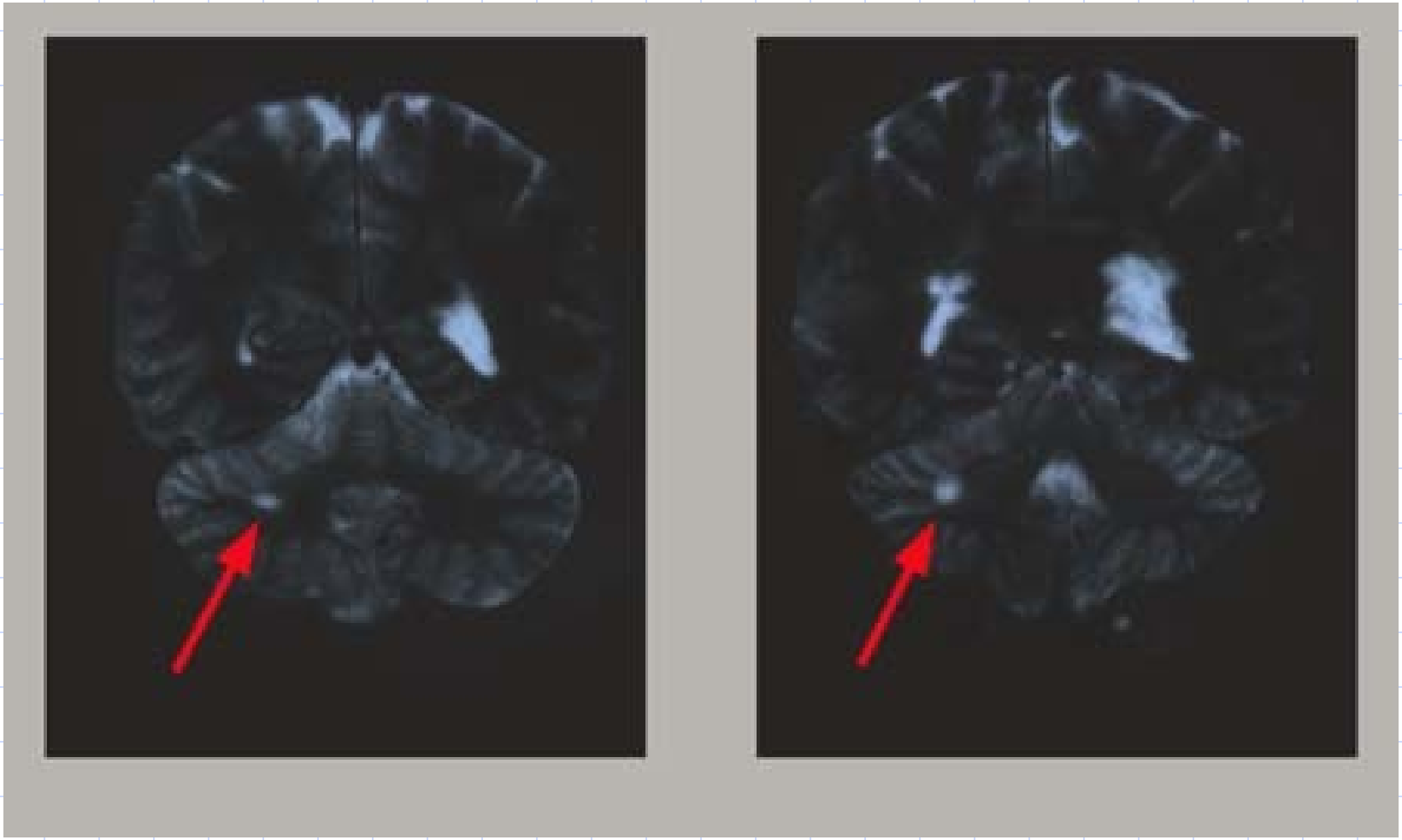
- MRI is abnormal in:
  - 90% of patients with definite MS
  - 70% of patients with probable MS
  - 30-50% of patients with possible MS

CRITERIA FOR MRI DIAGNOSIS OF MS

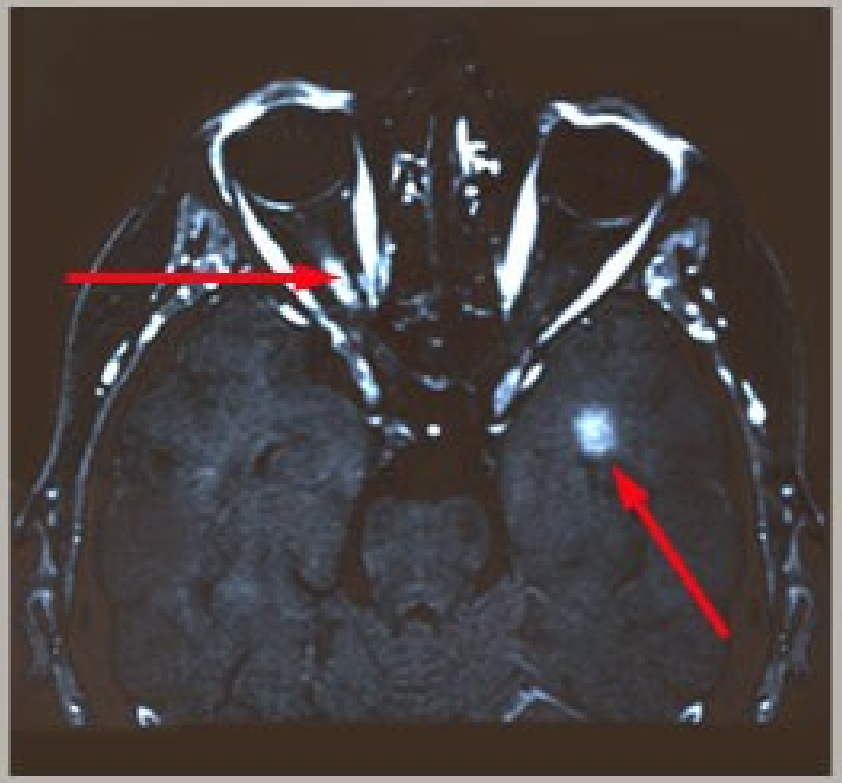
- Lesions abutting central ventricles
- Lesions with diameter of >0.6 cm
- Lesions in the posterior fossa

poor correlation between size and area of lesions and patient's disability

ABNORMAL MRI--CEREBELLUM



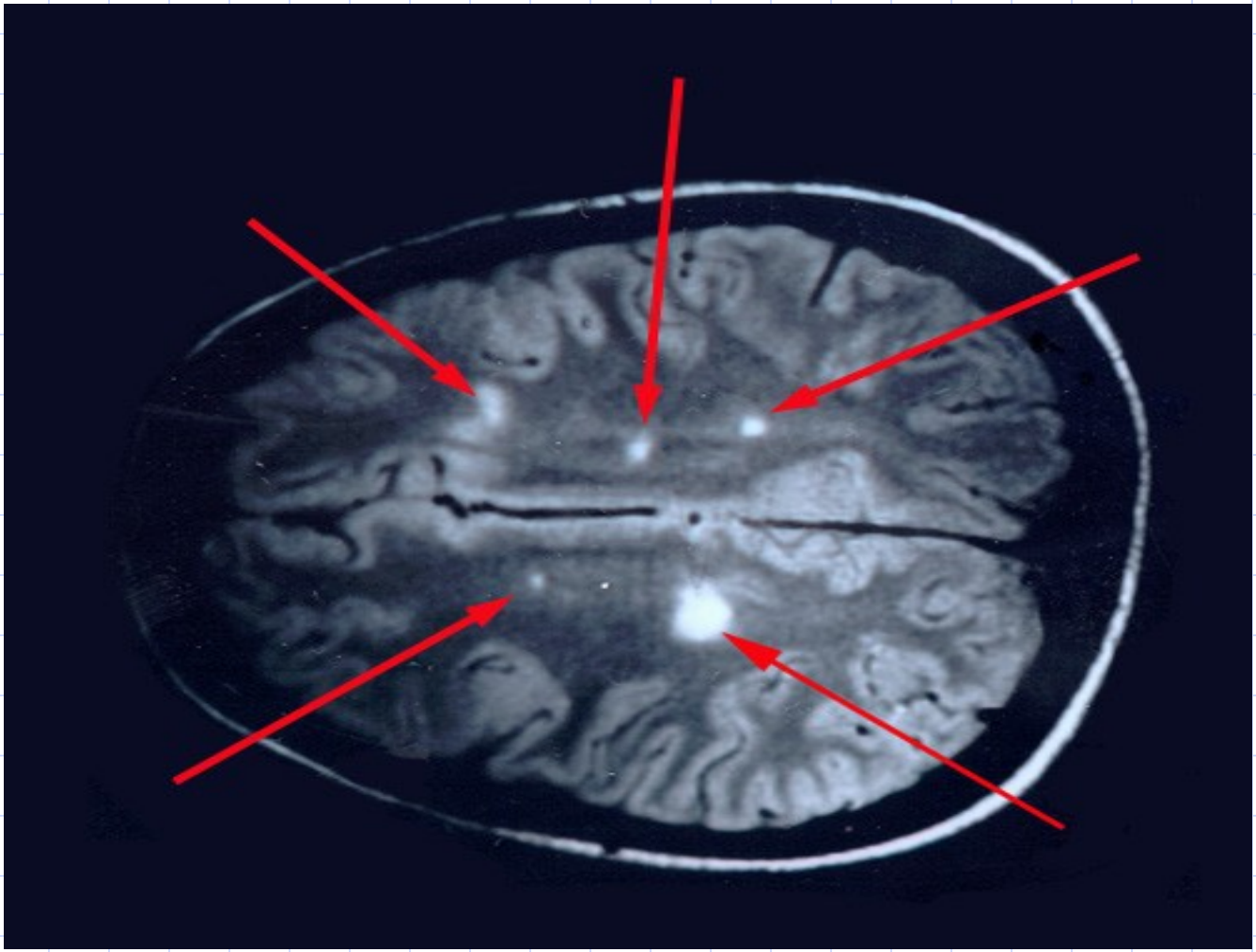
ABNORMAL MRI—OPTIC NERVE



This MRI scan from a patient with acute opticneuritis. This MRI scan shows enhancement of involved area in optic nerve (left top arrow).

A second area of contrast enhancement is seen in the contralateral lobe (right lower arrow).

ABNORMAL MRI—CEREBRAL HEMISPHERES



BLOOD AND URINE TESTS

- Unremarkable and nonspecific
- Attempts underway to identify myelin breakdown products in urine
- Monitor as indicated (suspected UTI / nephrotoxicity / medication side effects)

CLINICAL PRESENTATION

- Episodes of neurologic dysfunction followed by stabilization/remission
- Relapses can be rapid or gradual onset
- May persist or resolve over weeks to months
- Relapsing-remitting pattern is most common in MS

INITIAL SYMPTOMS

- Double vision / blurred vision
- Numbness/weakness in extremities
- Instability while walking
- Problems with bladder control
- Heat intolerance
- Motor weakness

****All symptoms can be precipitated by heat****

SENSORY DISTURBANCES

- Ascending numbness starting in feet
- Bilateral hand numbness
- Hemiparesthesia/dysesthesia
- Generalized heat intolerance
- Dorsal column signs
  - Loss of vibration/proprioception
  - Lhermitte’s sign

VISUAL DISTURBANCES

- Unilateral or bilateral partial/complete intranuclear ophthalmoplegia
- CN VI paresis
- Optic neuritis
  - Central scotoma, headache, change in color perception, retroorbital pain with eye movement)

MOTOR DISTURBANCES

- Weakness (mono-, para-, hemi- or quadriparesis)
- Increased spasticity
- Pathologic signs (Babinski, Chaddock, Hoffman)
- Dysarthria

OTHER CLINICAL SIGNS

- Urinary incontinence, incomplete emptying
  - Set up for UTI’s
- Cognitive and emotional abnormalities (depression, anxiety, emotional lability)
- Fatigue
- Sexual dysfunction

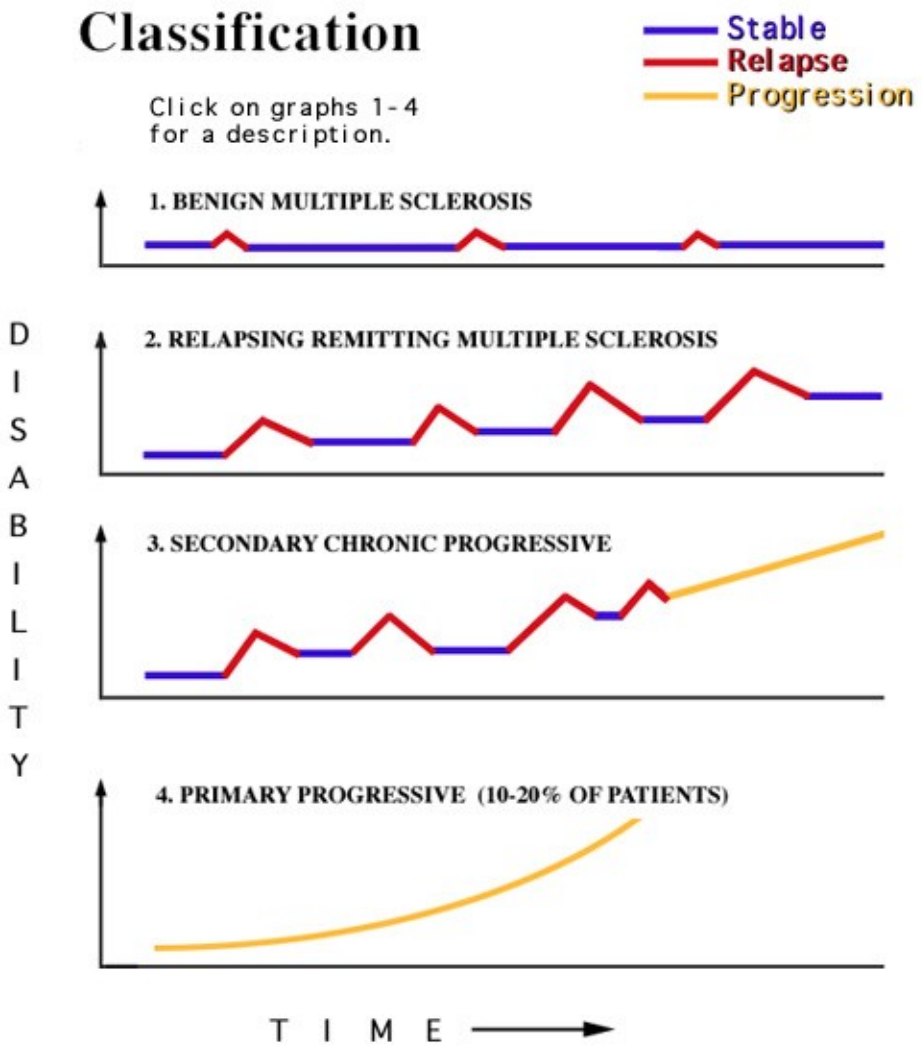
DIAGNOSTIC CRITERIA

- 2attacks with laboratory evidence but no clinical evidence = ***PROBABLE*** MS WITH LABORATORY SUPORT
- 2 attacks without lab abnormalities = CLINICALLY ***PROBABLE*** MS
- 2 attacks with clinical evidence and lab support = LAB SUPPORTED ***DEFINITE*** MS
- 2 attacks with clinical evidence of at least 2 lesions = CLINICALLY ***DEFINITE*** MS

TYPES OF MS

- Benign – 10%
- Relapsing-remitting – 40%
- Primary progressive – 10%
- Secondary chronic progressive – 40% of patients with originally relapsing-remitting course

COMPARATIVE GRAPHS



DIFFERENTIAL DIAGNOSIS

- Primary CNS vasculitis
- Postinfectious encephalomyelitis
- Lyme disease
- Behcet’s syndrome
- Sarcoidosis / Sjogren’s disease
- B12 deficiency / tertiary syphylis
- Leukodystrophies of adulthood

TREATMENT OPTIONS

- Exercise (avoid overheating)
- Physical / occupational therapy
- Nutrition (avoid extremes of weight)
- Avoid excess heat exposure or elevated core temperature
  - Prompt tx of fever with antipyretics
  - Cool environment / cool bath

MEDICAL THERAPY -- ACUTE

- Immunotherapy with steroids or ACTH
  - Suppress inflammatory response
  - Decrease severity/duration of exacerbations
  - Inhibit demyelinating process
  - IV (3-5 days), then oral taper
- Other immunomodulators (imuran, cytoxan, methotrexate)

MEDICAL THERAPY – RELAPSE PREVENTION

- Interferon 1-beta (Betaseron) or 1-alpha (Avonex), Copaxone (copolymer-1)
  - Useful for relapsing-remitting dz, not stable or progressive
  - Significant side effects (injection site rxn, nephrotoxicity, leukopenia)
  - Prevention of T-cell activation → decrease in relapse rate

MEDICATIONS ON THE HORIZON

- T-cell receptor peptides
- Anti-CD4 monoclonal antibodies
- Oral myelin
- Cladribine (selective toxicity for lymphocytes)
- IVIG
- Glatiramer acetate

SYMPTOMATIC THERAPY

- FATIGUE
  - Cool showers / baths
  - Amantadine (helpful in 40%)
  - Pemoline (CNS stimulant)
  - Fluoxetine or other SSRI’s

SYMPTOMATIC THERAPY – CON'TD

- VERTIGO

  ** Can last for hours to days **

  - Meclizine
  - Low dose valium / compazine
  - If associated with oscillopsia → baclofen, clonazepam
  - If associated with nausea/vomiting → reglan

SYMPTOMATIC THERAPY – CONT'D

- SPASTICITY
  - Baclofen → may cause muscle weakness; useful in spastic dysarthria
  - Valium → especially useful at night
  - Tizanidine (Zanaflex)

** can be very painful; most common in extensor muscles of lower limbs **

SYMPTOMATIC THERAPY – CONT'D

- PSYCHOLOGICAL PROBLEMS
  - TCAs (especially elavil)
  - SSRIs
  - Counseling

** suicide rate for MS patients is 7.5 times that of the general population **

SYMPTOMATIC THERAPY – CONT'D

- URINARY DYSFUNCTION
- Spastic bladder
  - Anticholinergics (oxybutynin, propantheline)
  - Baclofen, elavil
- Detrusor /ext. sphincter dyssynergia
  - Intermittent self-catheterization
  - Anti-cholinergics
  - Chronic indwelling catheter

OTHER SYMPTOMATIC TREATMENT

- SEXUAL ISSUES: multidisciplinary approach (meds, counseling)
- TREMOR: clonazepam, propranolol, diazepam
- PAIN (musculoskeletal abnormalities): neurontin, tegretol, depakote, TCA’s
- COGNITIVE DYSFUNCTION: neuropsych eval, rehabilitation, occupational therapy

PROGNOSIS

- EXTEMELY VARIABLE
- 50% chance of walking unaided 15 years after onset of disease
- Estimated longevity 25-35 years after diagnosis
- Common causes of death: secondary complications of immobility; depression (suicide)

FAVORABLE PROGNOSTIC FACTORS

- Female gender
- Low rate of relapses per year
- Complete recovery from 1st attack
- Long interval between 1st and 2nd attack
- Younger age of onset
- Later cerebellar involvement
- Low disability 2-5 years from dz onset

QUESTIONS?